UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/053,641	01/18/2002	Chieh-Sheng Lin	P1393	3585

7590 07/30/2002

LaRiviere, Grubman & Payne, LLP
P.O. Box 3140
Monterey, CA 93942

EXAMINER
SULLIVAN, DANIEL M

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 07/30/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/053,641	Applicant(s) LIN ET AL.
	Examiner Daniel Sullivan	Art Unit 1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-32 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-32 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This Office Action is a response to the Application and Information Disclosure Statement filed January 18, 2002. Claims 1-32 are pending in the application.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

1. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

2. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.185(a). Failure to take corrective action within the set (or extended) period will result in **ABANDONMENT** of the application.

The drawings are objected to for the reasons provided on the attached PTO 948, and because they contain amino acid and nucleotide sequences that are not identified by SEQ ID No.

A proposed drawing correction or corrected drawings are required in reply to the Office action to

avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Specification

The abstract of the disclosure is objected to because the brief description of figure 4 should read "the amino acid sequence thereof". Applicant is urged to review the entire disclosure for other typographical errors within the text. Correction is required. See MPEP § 608.01(b).

Claim Objections

Claim 20 is objected to because of the following informalities: the claim contains several typographical errors (i.e. missing articles in line 2, the phrase "in operable association" appears to be parenthetical and should therefore be set off with parentheses). Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4, 7, 11, 16, 19, 21 and 28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

The claims are drawn to a genus of promoters consisting of promoters isolated from the casein gene, whey acid protein gene, lactoalbumin gene, α-lactoalbumin gene, or lactoglobulin gene of human, pig, cattle, horse, goat, camel, sheep or rodent. The claimed genus is widely divergent, particularly with respect to those promoters that control expression of different genes, as differences in regulation of said genes (e.g. see Henninghausen et al. (1991) *Biotechnology* 16:65-74, especially Figure 6-1) indicates structural differences within the genes. The Revised Interim Guidelines state "when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus", "In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (Column 2, page 71436). The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species, by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics (see MPEP 2163 (ii)). In paragraph 0027 of the specification, "promoter" is defined as "a DNA sequence that is located at the 5' end of (i.e.,

precedes), a gene in a DNA polymer and provides a site for initiation of the transcription of the gene into mRNA", a list of preferred promoters is provided in paragraph 0032, and expression of hirudin from the α-lactoalbumin promoter is reduced to practice in EXAMPLES. The disclosure, including the Information Disclosure Statement, provides no guidance with respect to the structural features of the claimed promoters beyond that they can be found 5' to the indicated genes. This guidance is insufficient because the disclosure does not provide a description of the claimed genes, which would allow the skilled artisan to identify the promoters. An adequate written description of a DNA requires a description of the DNA itself. It is not sufficient to define DNA solely by its principal biological property, i.e. it "provides a site for initiation of the transcription of the gene into mRNA", because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any DNA with that biological property. Also, naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, claiming all DNA's that achieve a result without defining what means will do is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)).

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad class of *any* and *all* of the claimed promoters. Therefore, only the

described α-lactoalbumin promoter of pE-αLA-Hi vector, which was reduced to practice, meets the written description provision of 35 U.S.C. §112, first paragraph.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115). Therefore, although the art applied against the claims under 35 U.S.C. 102 and 103 below is enabling, its existence does not indicate that Applicant was in possession of the embodiments described in those publications.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6, 7, 9, 11, 14, 16-19, 27-29, 30 and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 6, 7, 9, 11, 14, 16, 18, 19 and 27-29 are drawn to expression vectors comprising various genes as promoters. Because the claims recite, "said promoter *is*...gene", the skilled artisan would interpret the claimed promoter to include the coding sequence as well as the region 5' to the coding sequence. The claims are indefinite because they are inconsistent with the description of promoter in the specification (paragraph 0027), which is defined as the DNA sequence located at the 5' end of a gene. This rejection can be traversed by amending the base claims so that they are drawn to promoters "*isolated from*...gene". In the interest of compact prosecution, the claims have been interpreted according to the definition of promoter provided in the specification.

With regard to claim 17, it appears that Applicant intends that the claim be drawn to a transgenic non-human mammal selected from the named species. As written, however, the claim is drawn to a transgenic mammal consisting of *all* of the named species. This rejection can be traversed by amending the claim to recite the limitation in proper Markush language.

With regard to claims 30 and 31, the claims are indefinite because they do not contain a transitional phrase (i.e. comprising, consisting of) to indicate whether the claimed sequences are opened or closed. This rejection can be traversed by amending the claims to read, "A polynucleotide... consisting of/comprising a nucleotide sequence selected from the group consisting of...".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 5, 8, 9, 12, 13, 14 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Houdebine et al. (1999; U.S. Patent No. 5,965,788).

Claims 1, 2 and 5 are drawn to an expression vector with a promoter specifically expressing nucleic acid encoding hirudin. Please note that the promoter of claim 1 is interpreted to be any promoter that could reasonably be expected to be active in a mammary gland cell, including constitutively active mammalian promoters such as those isolated from cytomegalovirus genes. Claim 2 limits the promoter of claim 1 to various mammary cell specific

promoters; and claim 5 limits the mammary gland cell or tissue of claim 1 to a cell or tissue from various mammals

Houdebine teaches a plasmid for transforming a mammary gland cell or tissue comprising a rabbit whey acid protein promoter (see especially beginning on column 6 through column 7, Examples 1 and 2) and that said plasmid can be used to express hirudin (see column 4, second full paragraph). Houdebine also teaches that the plasmid can be used to express a protein in the mammary gland cells of a mouse (see especially example 4). The plasmid taught by Houdebine is the same as the expression vector of the instant application.

Claims 8, 9 and 12 are drawn to a mammary gland cell transformed to express a nucleic acid encoding hirudin. Claim 9 limits the promoter controlling hirudin expression to one of several mammary gland specific promoters; and claim 12 limits the mammary gland cell to cells isolated from various species. Houdebine teaches production of a heterologous protein, including hirudin, under the control of the mammary gland specific whey acid protein promoter in the milk of a transgenic mouse comprising the plasmid described above (see especially column 7, example 4). The skilled artisan would appreciate that the presence of the heterologous protein in the milk of the transgenic animal indicates that the cells of the mammary gland are transformed to express said heterologous protein. The mammary gland cell taught by Houdebine is the same as the cell of the instant application.

Claims 13, 14 and 17 are drawn to a transgenic non-human mammal whose genome comprises a construct comprising a nucleic acid encoding hirudin operably linked to a promoter capable of expressing the nucleic acid in a mammary gland cell or tissue. Claim 14 limits the promoter to one of several mammary gland specific promoters, including the whey acid

promoter, and claim 17 limits the transgenic mammal to one of several species, including a rodent. Houdebine teaches a transgenic mouse whose genome comprises a construct, said construct comprising a heterologous protein, including hirudin, under the control of the mammary gland specific whey acid protein promoter (see especially column 7, example 3). The transgenic mouse taught by Houdebine is the same as the transgenic non-human mammal of the instant application.

The expression vector, mammary gland cell and transgenic non-human mammal taught by Houdebine are the same as those taught in the instant application, therefore the limitations of the claims are met by Houdebine.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 6-11, 13-16, 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Houdebine as applied to claims 1, 2, 8, 9, 13, and 14 above and in further view of Bleck et al (1993; WO 93/04165).

The limitations of claims 1, 2, 8, 9, 13 and 14 and the teachings of Houdebine are recited above. Claims 3 and 4 are drawn to the expression vector of claims 1 and 2, respectively, wherein the promoter is isolated from one of a variety of mammalian species, including bovine; claim 6 limits the promoter of claim 1 to an α-lactoalbumin promoter, and claim 7 further limits the α-lactoalbumin promoter of claim 6 to a promoter isolated from one of various mammalian

species, including bovine. Claims 10 and 11 are drawn to the transformed mammary gland cell of claim 8 and 9, respectively, wherein the promoter is isolated from one of a variety of mammalian species, including bovine. Claims 15 and 16 are drawn to the transgenic non-human mammal of claims 13 and 14, respectively wherein the promoter is isolated from one of a variety of mammalian species, including bovine. Claim 18 limits the promoter of claim 13 to an α-lactoalbumin promoter, and claim 19 further limits the α-lactoalbumin promoter of claim 18 to a promoter isolated from one of various mammalian species, including bovine.

Houdebine teaches all of the limitations of the claims except for a mammalian α-lactoalbumin promoter. Bleck teaches the expression of a heterologous protein in the mammary gland of a transgenic mouse, wherein expression of said heterologous protein is under the control of the bovine α-lactoalbumin promoter (see especially page 3, paragraph 4; page 7, third full paragraph; and Example 1, pages 18-22). It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Houdebine to include the bovine α-lactoalbumin promoter taught by Bleck to provide a vector, mammary gland cell, and transgenic mammal according to the present Application. The teachings can be easily combined by substituting the α-lactoalbumin promoter taught by Bleck for the whey acid protein promoter taught by Houdebine. Motivation to combine these teachings can be found in Bleck, who teaches that the α-lactoalbumin promoter is preferred because it "exerts the tightest lactational control of all milk proteins. Further it is independently regulated from other milk proteins and is produced in large quantity by lactating animals" (page 8, paragraph 1). The skilled artisan would have a reasonable expectation of success in combining these teachings because Bleck teaches that the α-

lactoalbumin promoter is active in mouse and therefore would work in the specific embodiment enabled by Houdebine.

Claims 1-5, 8-17 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoo et al. (2000; WO 00/15808) in view of Liersch et al. (1995; 5,422,249).

The limitations of claims 1-5 and 8-17 are recited above. Yoo teaches an expression vector comprising a goat β-casein gene promoter according to claims 1-4 of the instant application (see especially "Construction of Expression Vectors" pages 5-7), for expression in mouse mammary gland derived HC11 cells according to claims 5 and 8-12 (see especially beginning on page 8, last paragraph through page 10, first paragraph; and beginning on page 19, Example V). Yoo also teaches a transgenic mouse comprising the expression vector described above according to claims 13-17 of the instant application (see especially beginning on page 10, "Expression in Transgenic Mouse"; and Example VIII beginning on page 22). Yoo teaches all of the limitations of the claims except the expression of a hirudin transgene. Liersch teaches a cDNA encoding hirudin and heterologous expression of said cDNA in bacteria and yeast. It would have been obvious to the skilled artisan to modify the teachings of Hwang to include the hirudin cDNA taught by Liersch for the purpose of producing hirudin from mammalian mammary glands. Motivation to combine these teachings comes from Yoo, who teaches several advantages of heterologous production of proteins in mammary glands including: high level expression leading to low production cost, easy scale up for the mass-production of target proteins; and relatively low complexity and toxicity of endogenous protein secreted from mammary gland tissue (see especially beginning on page 23, final paragraph through page 24,

second full paragraph). Motivation also comes from Liersch who teaches that the limited availability of hirudin is a serous limitation on its use in medicine in spite of excellent biological properties (see column 2, first full paragraph). One would have a reasonable expectation of success in combining these teachings in light of the wide variety of proteins that have been successfully expressed in mammary glands of transgenic animals (e.g. see Heyneker et al (1991; WO 91/08216) beginning on page 3, paragraph 1 through page 4, final paragraph and citations therein).

Claim 32 is drawn to a method of producing hirudin, comprising steps of: culturing transformed mammary cells with the expression vector of claim 1, and recovering the hirudin expressed by said transformed mammary cells. As described above, Yoo teaches expression of a heterologous protein in transformed mammary gland cell line. Yoo does not teach heterologous expression and recovery of hirudin. Liersch teaches heterologous expression and recovery of hirudin (see especially beginning column 20, final paragraph through column 21). Motivation to combine these teachings comes from Liersch regarding the need for improved availability of hirudin and from Yoo, who teaches that, "The proteins produced in mammary gland tissue-derived cells...are few in number, so that the target protein is easy to isolate and purify".

Claims 1-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johnson (1998; WO 98/35689) in view of Liersch.

The limitations of claims 1-19 are recited above. Claims 20-29 are drawn to a mammalian cell isolated from the transgenic non-human mammal of claim 13. Claim 21 limits the promoter of claim 20 to one of several mammary gland specific promoters; claim 22 and 23

limit the promoters of claim 20 and 21, respectively, to a promoter isolated from various mammalian species; claim 24 limits the cell of claim 20 to a cell isolated from one of several mammalian species; and claims 25 and 26 limit the cell of claims 20 and 21 to a mammary gland cell. Claim 27 limits the promoter of claim 20 to an α-lactoalbumin promoter; claim 28 further limits the α-lactoalbumin promoter of claim 27 to a promoter isolated from various mammalian species; and claim 29 limits the cell of claim 27 to a mammary gland cell. Johnson teaches an expression vector for transforming a mammary gland cell or tissue (see especially beginning on page 27, Example 1; and beginning on page 33, Example 3), a transformed mammary gland cell containing a nucleic acid that expresses a heterologous protein (see especially beginning on page 39, Example 7), a transgenic non-human mammal comprising a DNA sequence encoding a heterologous protein and expressing said heterologous protein in a mammary gland cell or tissue (see especially beginning on page 32, Example 2; and beginning on page 34, Example 4); and a mammalian cell isolated from a transgenic non-human mammal comprising a construct comprising a DNA molecule encoding a heterologous protein operably linked to a promoter (see especially page 23, lines 35-38 and continued on page 24, line 1). On page 9, lines 26-31, Johnson also teaches that a whey acid protein promoter, various casein promoters, α-lactoalbumin promoter or β-lactoglobin promoter can be used in the vector to express a heterologous protein in the cells and animals described above. On page 19, lines 19-27, Johnson teaches that the whey acid protein and casein promoters can be obtained from rodent, and that the casein, α-lactoalbumin, and β-lactoglobin promoters can be obtained from porcine, bovine, equine, ovine, rabbits, rodents, dogs and cats. Finally, Johnson teaches that the transgenic animals, and by extension the isolated cells obtained from said animals, can be pigs, goats,

sheep, cows, horses, rabbits, rodents, cats and dogs (see page 13, lines 12-15). Johnson teaches all of the limitations of the claims except the expression of a hirudin transgene. Liersch teaches a cDNA encoding hirudin and heterologous expression of said cDNA in bacteria and yeast. It would have been obvious to the skilled artisan to modify the teachings of Hwang to include the hirudin cDNA taught by Liersch for the purpose of producing hirudin from mammalian mammary glands. Motivation to combine these teachings comes from Yoo, who teaches several advantages of heterologous production of proteins in mammary glands as described above. Also as described above, motivation comes from Liersch who teaches that the limited availability of hirudin is a serious limitation on its use in medicine in spite of excellent biological properties. One would have a reasonable expectation of success in combining these teachings in light of the wide variety of proteins that have been successfully expressed in mammary glands of transgenic animals (e.g. see Heyneker et al (1991; WO 91/08216) beginning on page 3, paragraph 1 through page 4, final paragraph and citations therein).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on 703-305-1998. The fax phone numbers for the

organization where this application or proceeding is assigned are 703-746-9105 for regular communications and 703-746-9105 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

dms
July 24, 2002

JAMES KETTER
PRIMARY EXAMINER